Docket No.: 511582002420
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:
Aya JAKOBOVITS et al.

Application No.: 10/001,469

Filed: October 31, 2001

For: NUCLEIC ACID AND CORRESPONDING PROTEIN ENTITLED 101P3A11 USEFUL IN TREATMENT AND DETECTION OF CANCER

Confirmation No.: 3304

Art Unit: 1642

Examiner: Minh-Tam B. Davis

BRIEF ON APPEAL

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A Notice of Appeal was filed in this case on 9 June 2005, making an appeal brief initially due 9 August 2005. A petition for an extension of time of five (5) months until 9 January 2006 is enclosed along with the required fee. The rejection of all pending claims, claims 48, 50, 54 and 55 is appealed.

The Brief contains the sections required by 37 C.F.R. § 41.37.

1. Real Party in Interest

The Real Party in Interest is the assignee herein Agensys, Inc., located in Santa Monica, California.

2. Related Appeals and Interferences

No related appeals and interferences that would affect or be directly affected by or have a bearing on the Board's decision in this appeal are known to the appellant, appellant's representative, or the assignee.

3. Status of Claims

The application contained 47 claims as filed. All of claims 1-47 were canceled in a Preliminary Amendment submitted 16 August 2002 and claims 48-50 were added. In a response to an initial Restriction Requirement, claim 49 was canceled, claim 48 was amended and claims 51-52 were added. A second Restriction Requirement resulted in amending claim 48, canceling claims 51-52 and adding new claim 53. In response to an initial substantive Office action, claim 53 was canceled and claims 54-56 were added. In response to a final Office action, claim 48 was amended and claim 56 was canceled.

In summary, of 56 claims in the case at one time or another, claims 1-47, 49, 51-53 and 56 have been canceled and the remaining claims, claims 48, 50, 54 and 55 are on appeal.

4. Status of Amendments

It is understood that the amendment proposed after final rejection was entered. The Examiner refused to enter the amendment in an Advisory Action mailed 17 June 2005; appellant

petitioned on 10 August 2005 to have the amendment entered , and it is understood from a telephone conversation with William Dixen on 6 January 2006 that this petition has been granted. Therefore, it is believed that the amendment after final has been entered.

5. Summary of Claimed Subject Matter

The claims are essentially directed to a screening method to identify an agent that decreases the activity of a specific protein which is the product of the gene designated 101P3A11, and has the amino acid sequence of SEQ ID NO: 2866. This gene has also been designated PHOR-1 (page 5, lines 25-28) and as this is a simpler term, that term will sometimes be used in the present brief. The screening methods now claimed are supported at least in original claim 31 as filed which was directed to

> A method to identify an anticancer agent for use in humans which method comprises
>
> providing cells which have been modified to contain an expression system for 101P3A11 protein...
>
> the steps are essentially those as provided in present claim 48.

The recognition that inhibiting the activity of the PHOR-1 protein would be useful in cancer treatment is set forth, for example, on page 5, lines 23-25. (A substitute specification was filed in this case on 23 February 2004 and citations refer to locations in this document.) Page 63, lines 1-2 (under Section XII) also indicate that the treatments would involve inhibiting the function of the PHOR-1 protein. Further, Example 31 describes methods for identifying molecules that interact with PHOR-1 (in this case only binding). Particular activities to be assessed in claim 48 (cAMP accumulation or the downstream signaling effects thereof) are described in detail in Example 40.

The specific activity set forth in claim 55 – PHOR-1 mediated ERK phosphorylation - is described in this example as well.

6. Grounds of Rejection to be Reviewed on Appeal

The final rejection contained an objection to claim terminology and a rejection under 35 U.S.C. § 112, paragraph 2. In view of the grant of the Petition to enter the amendment responsive to the Office action that includes this objection and paragraph 2 rejection which amendment addressed these specifically, it appears there is only one rejection outstanding to be argued on appeal. This rejection is made under 35 U.S.C. § 112, first paragraph, on the basis that claims 48, 50, 54 and 55 are assertedly not enabled. One aspect of even this rejection – that it was unclear whether the claimed protein was limited to SEQ ID NO: 2866 - is apparently overcome by the entry of the amendment. The remaining aspects of the rejection are still outstanding. Essentially, the rejection is as follows:

> The specification is not enabled for a method for identifying an agent that decreases 101P3A11 protein activity, or a method for identifying an agent that decreases 101P3A11-mediated ERK phosphorylation or 101P3A11-mediated cAMP accumulation....

and that

> One would not know how to use the agents identified by the claimed method.

7. Argument

A portion of this rejection is clearly misplaced in that the Examiner asserts that there is no definition of "101P3A11 protein activity" in the specification. However, as noted above, this is not the case and the claims as amended specifically identify the activity as the accumulation of cAMP

in the cells or the downstream signaling effects of this accumulation, including the specific downstream signaling effect of ERK phosphorylation as set forth in claim 55.

The basis of the substance of the rejection is that because the data set forth in the specification relate only to *in vitro* tests, it is not possible to extrapolate these results to usefulness in treating proliferative diseases because, according to the Examiner, there is inadequate proof that the identified agents will eventually prove thus useful. There appears to be no assertion that it would be beyond the capabilities of the ordinarily skilled artisan to measure an increase in cAMP activity or a change in ERK phosphorylation. These are standard techniques well known to every practitioner in this field. Essentially, then, the rejection for lack of enablement is based on an asserted lack of utility. Phrased in terms of the guidelines provided by the Office, there appears to be no contention that the screening method is not specific or not substantive, but rather that the utility for the identified molecules is not credible. The asserted lack of credibility is addressed as follows:*

(a) The rejection for lack of enablement is indeed a utility rejection.

Although the Advisory Action states that "it is noted that this is not a utility rejection," appellants are at a loss to determine what else it might be. Specifically, the Advisory Action states "since one would not know how to use the screened agent, based on their (sic) property of

* For clarity, appellants note that the original bases for rejection for asserted lack of enablement were overcome by amendment. The claims as presented originally were directed to a method to identify an agent that decreases the "expression status of 101P3A11" and did not identify 101P3A11 protein by a SEQ ID NO. The rejections based on enablement were that one does not know what constitutes "expression status" or "at least one property characteristic of the expression status" (also in the original claim); an objection that one cannot determine what other proteins are associated with 101P3A11 (a feature of claim 53, now canceled) and an objection that "variants" of 101P3A11 are included (now no longer the case). Since the entire rationale for the originally formulated rejection under § 112, first paragraph, has been removed by amendment, and the rationale for the rejection was completely revised in the Final Office action, appellants address only the rejection as it currently stands.

decreasing 101P3 (sic) protein activity ... one would not know how to used the claimed method." This appears to be the entire basis for the rejection.

(b) It is irrelevant whether the activities of the protein assessed in the screening method are those directly associated with cancer progression.

The Advisory Action states that there is no correlation between inhibition of the cAMP accumulation or ERK phosphorylation mediated by the PHOR-1 protein in any disease, and therefore one does not know how to use the screened agent that inhibits the cAMP accumulation or ERK phosphorylation for therapeutic purposes. This is not the point. The cAMP accumulation and ERK phosphorylation are simply activities of the PHOR-1 protein that can readily be assessed, it does not necessarily follow or need to follow that it is these activities that are responsible for the involvement of the PHOR-1 protein in cancer progression. They are just used as methods to evaluate the activity of the protein. While it is likely that these activities *are* those associated with cancer progression, their value as measurement tools does not depend on the mechanism by which the PHOR-1 protein encourages the progression of cancer. Compounds that inhibit these activities would be likely to inhibit any other activity of the protein as well.

(c) The Examiner has not established a *prima facie* case that the asserted utility of the screening test that is the subject of the claims is incredible.

The first objection raised is based on an article by Chang, F., *et al., Leukemia* (2003) 17:1263-1293 which is quoted for the proposition that the pathway on which ERK kinase exists is complex and may not be associated with the role (if any) of PHOR-1 protein in cancer progression. What Chang actually states is that this pathway is indeed linked to transcription factors. Whether the mechanism of PHOR-1 cancer progression mediation involves ERK phosphorylation is

irrelevant to evaluating utility, as noted above. In light of other evidence that PHOR-1 is involved in cancer progression *per se*, the nature of the mechanism is not germane. Again, the ERK phosphorylation effect is used as an assay method, not necessarily as a mechanism for controlling cancer cell growth.

The second point raised by the Examiner is that the *in vitro* data in the specification cannot be extrapolated to an *in vivo* environment. In support of this position, two papers are cited: Hummler, E., *et al., PNAS* (1994) 91:5647-5651 and Xu, X., *et al., FASEB J* (2001) 15:A313.

The Hummler paper is said to demonstrate the importance of homeostatic mechanisms in an *in vivo* context. However, this paper presents a more complicated picture. Apparently, the block of CREB function in transgenic mice does have physiological effects (page 5647, left-hand column). It is only in CREB-deleted mice that are generated from embryonic stem cells that appear to have a compensating mechanism. In any case, this specific instance of one aspect of a complex pathway and a differing effect *in vivo* is not determinative with regard to the vast majority of instances where *in vitro* data are highly relevant.

The Xu abstract is solely concerned with *in vitro* studies. There *was* a measured effect exerted by the presence of IRF-1 in cells derived from mice which produce this protein. "There was a greatly decreased cell surface expression of FAS and FASL on $CD4^+$ T cells of IRF-1 null mice compared to IRF-1-+/+ mice..."; only proliferation kinetics and apoptosis were similar. Again, there is no question that in some cases compensatory mechanisms may exist *in vivo*; this does not seem to have deterred the industry in general from utilizing *in vitro* screens to provide initial candidates which can further be tested *in vivo*.

Appellants question whether merely demonstrating that *in vitro* results are not always reflected *in vivo* is sufficient to undermine the credibility of a utility based on overexpression of PHOR1 protein in cancer and evidence that the protein enhances proliferation.

(d) There is ample evidence of record that the screening test claimed is useful.

The rejection does not take account even of all the evidence presented in the specification itself. Only the data indicating that PHOR-1 phosphorylates ERK *in vitro* is acknowledged. But there are additional data in the specification that are even more relevant. Enhancement of proliferation which is the direct effect of the PHOR-1 protein on tumor progression is demonstrated in Example 42. It was there demonstrated that the PHOR-1 protein imparts a growth advantage on NIH-3T3 cells (as shown in Figure 37) and that the PHOR-1 protein induces colony formation with over 100-fold increase relative to controls (as shown in Figure 43).

In Example 32, the effect of the PHOR-1 protein on tumor growth *in vivo* is demonstrated. As noted, Figure 21 compares the subcutaneous growth of control 3-T-3 cells and 3-T-3 cells that contain an expression system for PHOR-1 protein. Figure 42 compares such growth with tumors that are implanted by surgical orthotopic methods. In both cases, the tumor cells that contain PHOR-1 protein proliferate *in vivo* more aggressively.

Finally, appellant believes it is appropriate to consider the submitted copy of the Declaration of Steven Kanner originally submitted in a related application, U.S. 10/147,368. The results of the experiment described show definitively that a monoclonal antibody to the PHOR-1 protein inhibits the growth of tumors *in vivo*. This Declaration was not considered by the Examiner because the amendment was not entered; however, in view of the grant of the Petition to enter the amendment, consideration of this Declaration is believed proper. It is contained in the Evidence Appendix.

As the Board is no doubt aware, most cases dealing with utility in a pharmaceutical context are concerned with claims directed to compounds or classes of compounds asserted to have a particular therapeutic effect. That is not the question raised here. The question raised as to utility here is whether compounds which demonstrably (as will be ascertained in the claimed assay) inhibit PHOR-1 protein function, would be useful in treating cancers in which proliferation is mediated by this protein.

It does not appear that the Office has, in the past, had any difficulty in acknowledging utility based on a nexus between a particular inhibition activity and a therapeutic effect. A case relevant to this issue is *Ex Parte Bhide*, 42 USPQ 2d 1441 (BPAI 1996). In this case, claims were directed to certain novel compounds and the ultimate utility claimed was the treatment of cancer. The applicants had asserted that the basis for efficacy in treating cancer was the ability of their compounds to inhibit farnesyl protein transferase, which putatively effects the binding of cancer related *ras* proteins to membranes. The Examiner rejected the claims as lacking utility because only the treatment of cancer was disclosed as a utility and this is assertedly unpredictable without evidence. The applicants asserted the disclosure of a Brown patent which taught that farnesyl transferase enzymes were involved in the transfer of farnesyl groups to the oncogenic *ras* protein.

The Board cited black letter law that unless there is a reason for one skilled in the art to question the objective truth of the statement of utility in the specification, the specification should be taken as sufficient to satisfy the utility requirement. *In re Brana*, 51 F3d 1560, 34 USPQ2d 1436 (Fed Cir 1995); *In re Marzocchi*, 439 F2d 220; 160 USPQ 367 (CCPA 1971). The Board acknowledged that if there is a reason for one skilled in the art to question the objective truth of the statement of utility, a rejection would be proper. *In re Langer*, 503 F2d 1380, 183 USPQ 288

(CCPA 1974). The Board in this case found that the Brown patent made it clear that there was a "recognized relationship between inhibition of farnesyl protein transferase in uncontrolled cell growth – which is what cancer is all about" and therefore that the statement that "cancer may be treated with compounds which inhibit farnesyl protein transferase is not inherently incredible."

The Board did affirm the rejection, but on the very different basis that the disclosed compounds seemed to lack the recognized structural requirement for such inhibition.

So in the present case, the issue is not whether there are any compounds disclosed that would successfully treat cancer, but rather whether compounds identified a test designed to identify compounds that inhibit PHOR-1 protein activity would be useful in cancer treatment. Appellants submit that there is ample evidence in the specification itself that this is credible, and this evidence has been set forth above – it is shown that the PHOR-1 protein enhances proliferation of cancer cells *in vivo* and *in vitro* and the Declaration of Dr. Kanner establishes that inhibition of this protein *in vivo* inhibits the growth of cancer.

(e) Conclusion

There is no assertion by the Examiner that the specification does not provide sufficient instruction to permit the skilled artisan to carry out the steps in the claimed method. Specific examples are provided for assessing cAMP accumulation and ERK phosphorylation, for example, in Example 40 of the specification, on pages 133-134. Although the Examiner denies this, it is clear that the "lack of enablement" rejection is based on asserted lack of utility for any compound that is identified using the screening method. The Examiner appears to consider this utility to lack credibility because, in the Examiner's view, the data provided by applicants are insufficient to demonstrate that the PHOR-1 protein has a role in tumor progression. It is respectfully submitted

that more than adequate evidence exists in the specification, since the presence of an expression system for this protein in tumor cells enhances their proliferation both *in vitro* and *in vivo*. In addition, the Declaration of Steven Kanner demonstrates that tumor growth *in vivo* can be inhibited by an antibody directed to this protein. Appellants believe that these data should clearly suffice to show that inhibitors of this protein are excellent candidates as therapeutic compounds to arrest the growth of tumors that contain PHOR-1this protein. As the Guidelines promulgated by the Office make clear, the benefits to the public of the invention need not be so immediate that one could simply go out and purchase a claimed product.

As noted in MPEP § 2701.01 1(b) on page 2100-33 of the August 2005 edition,

> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement (cited *Brenner v. Manson*) rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

This is the case here, where compounds not yet identified using the methods of the invention may not be currently available, but they can certainly be identified using the methods of the invention and their utility once they are identified has been specified.

8. Claims Appendix

An Appendix containing a copy of the claims as currently pending is attached.

9. Evidence Appendix

Attached is the Declaration under 37 C.F.R. § 1.132 of Steven Kanner is attached hereto.

10. Related Proceedings Appendix

No related proceedings are referenced in paragraph 2. above, therefore no Appendix is included.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: January 9, 2006 By: Kate H. Murashige

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130-2040
Telephone: (858) 720-5112
Facsimile: (858) 720-5125

CLAIMS APPENDIX

1-47. (canceled)

48. (previously presented): A method to identify an agent that decreases 101P3A11 protein activity, comprising:

providing a first sample of cells and a second sample of cells, wherein the cells of each sample express 101P3A11;

contacting the first sample with a candidate compound and

measuring 101P3A11 protein activity in the first sample with the candidate compound;

measuring 101P3A11 protein activity in the second sample, wherein the second sample has not been contacted with said candidate compound;

comparing the measured 101P3A11 protein activity in said first and second samples;

whereby a diminution in the 101P3A11 protein activity in said first sample as compared to said second sample identifies said compound as an agent that decreases 101P3A11 protein activity;

wherein 101P3A11 protein is SEQ ID NO: 2866; and

wherein said activity comprises 101P3A11-mediated cAMP accumulation or the downstream signaling effects thereof.

49. (canceled)

50. (previously presented): The method of claim 48, wherein said cells have been modified to contain an expression system for said 101P3A11 protein.

51-53. (canceled)

54. (previously presented): The method of claim 48, wherein the candidate compound is an antibody that binds specifically to the 101P3A11 protein.

55. (previously presented): The method of claim 48, wherein measuring the 101P3A11 activity comprises measuring a downstream signaling effect which is 101P3A11-mediated ERK phosphorylation.

56. (canceled)

EVIDENCE APPENDIX

This appendix contains, for the convenience of the Office, the following evidentiary material already of record:

1. Declaration of Steven Kanner (submitted with the Response filed 16 February 2005.

Docket No.: 511582002421
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Aya JAKOBOVITS et al.

Application No.: 10/147,368

Filed: May 15, 2002

For: NUCLEIC ACIDS AND CORRESPONDING PROTEINS ENTITLED 101P3A11 OR PHOR-1 USEFUL IN TREATMENT AND DETECTION OF CANCER

Art Unit: 1642

Examiner: Minh-Tam B. Davis

DECLARATION OF DR. STEVEN B. KANNER

UNDER 37 C.F.R. § 1.132

Commissioner for Patents

Alexandria, VA 22313-1450

Dear Sir:

I, Steven B. Kanner, declare as follows:

1. I am Director, Cancer Research, at Agensys, the assignee of the present application. I am actively engaged in efforts to determine efficacy of antibody-based treatments for cancer. A copy of my current *curriculum vitae* is attached hereto as Exhibit A.

2. Along with my colleagues, I undertook an experiment to demonstrate the ability of antibodies immunoreactive with 101P3A11 v. 1 to inhibit the growth of tumors *in vivo* in mice. In these experiments, groups of SCID mice were injected subcutaneously with 2,000,000 prostate

cancer cells per mouse. There were five treatment groups with between 7-10 mice per group. Control groups received either PBS or KLH MAb, and test groups received either M3/47(3)24, a monoclonal antibody generated to the N-terminal peptide of 101P3A11 v. 1 containing amino acids 1-23 with an added linker (MVDPNGNESSATYFILIGLPGLESGSGC); M3/47(3)2, a monoclonal antibody raised against the N-terminal peptide of 101P3A11 v. 1 containing amino acids 1-23 with an added linker (MVDPNGNESSATYFILIGLPGLESGSGC); or M1/1G8, a monoclonal antibody generated against the Prostate Stem Cell Antigen. Treatment with antibodies started on the same day as tumor cell injection, and injections were repeated twice a week for a total of 12 doses of 250 μg administered IP. Tumor growth was followed over a period of 40 days.

3. The results are shown on the attached Exhibit B. As shown, after 40 days, the control group receiving PBS showed tumor volumes of almost 800 mm^3, while those provided MAb M3/47(3)24 showed tumor volumes of only 200 mm^3. The other monoclonal antibody directed to 101P3A11, M3/47(3)2, is less effective, but nevertheless slightly lower than at least the PBS control. It appears to have no statistical difference to the control KLH MAb. Two possible reasons that could account for the difference in efficacy between MAb M3/47(3)24 and its sister antibody M3/47(3)2 are: 1) differences in its epitope specificity and/or 2) its relative affinity for 101P3A11. Generally, monoclonal antibodies that are raised to the same antigen can differ in epitope specificity and relative affinity. Accordingly, these properties are unique to each antibody.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that

such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Santa Monica, California on January 17, 2005.

Steven B. Kanner

STEVEN BRIAN KANNER, PH.D.

Agensys, Inc.
1545 17th Street
Santa Monica, CA 90404
Phone: 310.820.8029 (ext. 104)
Fax: 310.820.8489
E-mail: skanner@agensys.com

PROFILE

Pharmaceutical/Biotechnology research leader with extensive experience in novel target identification and validation, screen development and both small molecule drug and antibody discovery, with expertise in oncology, immunology and inflammation. Self-motivated strategic planner, skilled in motivating, developing, hiring, managing and building scientific teams to expedite novel drug/therapeutic candidate discovery for clinical trial consideration.

PROFESSIONAL EXPERIENCE

AGENSYS, INC. **2003 -**
Santa Monica, CA

Director, Cancer Research

Direct a research group including 19 scientists (Ph.D. and research associates) to identify, validate and develop novel targets for the generation of new therapeutics for cancer. Prioritize in-house portfolio for evaluation of targets for either monoclonal antibody development or for alliances for small molecule development or vaccine generation. Report to the Chief Scientific Officer.

- Establish teams for the validation of targets using RNAi knockdown technologies and over-expression systems to evaluate novel genes for establishing new monoclonal antibody based cancer therapies
- Serve on joint oversight committees with outside collaborators on alliances for propritetary targets to develop monoclonal antibodies, small molecule and vaccine approaches

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE **1990 - 2003**
Princeton, NJ (in Seattle, WA from 1990-1997)

Associate Director, Immunology and Oncology Drug Discovery (1999 - 2003)

Directed a research group including 25 scientists (Ph.D. level and research associates) to identify, validate and develop novel targets for therapeutic intervention in both immunological/inflammatory diseases and cancer. Managed annual research budget for group ($250K) for laboratory operations, travel and training of scientific staff. Senior leader guiding the direction of the research effort in all pre-clinical drug discovery phases, including administrative functions, reporting to the Vice President of Immunology and Oncology Drug Discovery.

- Established a research group to identify novel targets for therapeutic intervention in both immunological/inflammatory diseases and cancer. Group developed reagents, assays, screens and analyses on over fifteen targets for future drug discovery projects
- Validated novel targets through bioinformatics, microarray technologies, Taqman for expression profiling, transgenic mouse development and analysis, flow cytometry, full-length cloning, monoclonal antibody generation and general protein expression/purification
- Generated eight new screening assays (enzymes, protein-protein interactions, receptor systems) in 1.5 years with reduced cycle time (3-6 month turnaround time) from target validation to screening campaign
- Transitioned an early-phase project on Itk kinase to full-phase status in 1999 (screening campaign, lead identification, followed by significant chemistry support for SAR), taking a small molecule inhibitor to preclinical animal model testing stages and identifying efficacious compounds
- In-licensed a project on p38 from an external partner at an early phase, then transitioned it to full-phase status (1999). Developed a small molecule drug candidate (2001) for IND toxicology and phase I study
- Developed a Src kinase project (1997-2000) in immunology before transitioning program to Oncology, with discovery of an optimized small molecule currently ready for phase I studies
- Co-chaired the Exelixis Oncology alliance, established to identify new targets for cancer. Nine new targets for oncology were identified in 1.5 years, and three high throughput assays were established
- Served on immunology/inflammation licensing team for identifying outside opportunities, and served on pulmonary licensing team and subcommittees for early-stage external technologies. Efforts led to the in-licensing of the p38 project and licenses for using inflammatory target technologies

Principal Scientist, Immunological Diseases (1997 - 1999)

Established a Signal Transduction group to identify small molecule therapeutics to treat immunological and inflammatory disorders. Group included 4 Ph.D. level investigators and 11 associate scientists involved in projects relating to targeting intracellular signaling components for identification of new drug candidates

Senior Research Investigator II, Immunodeficiency and Immunomodulation (1993 - 1997)
Seattle, WA (former Oncogen biotechnology company purchased by Bristol-Myers Squibb Company)

Senior Research Investigator I, Immunodeficiency and Immunomodulation (1990 - 1993)
Seattle, WA (former Oncogen biotechnology company purchased by Bristol-Myers Squibb Company)

UNIVERSITY OF VIRGINIA, DEPARTMENT OF MICROBIOLOGY AND CANCER CENTER **1986 - 1990**
Charlottesville, VA

Postdoctoral fellow, Oncology (advisor: J. Thomas Parsons, Ph.D.)

- Identified novel mechanisms of $p60^{src}$ activation in carcinogen-transformed embryonic cells
- Discovered novel tyrosine-phosphoyrlated substrates of the $p60^{src}$ oncogene by monoclonal antibody generation and biochemical characterization
- Commercialized monoclonal antibodies to FAK, tensin, $p120^{ctn}$, $pp60^{src}$, phosphotyrosine and cortactin

EDUCATION

Ph.D.	University of Miami (Immunology and Microbiology)	**1986**
B.A.	University of California, Berkeley (Genetics)	**1980**

HONORS, AWARDS, SCHOLARSHIPS AND FELLOWSHIPS

Bristol-Myers Squibb Excellence Awards	**1996 - 2002**
NIH Postdoctoral Fellowship Grant (F32-CA08316), University of Virginia	**1987 - 1990**
Presidential Scholarship, University of Miami	**1981 - 1986**
Honor Society, University of California, Berkeley	**1978 - 1980**

PROFESSIONAL AFFILIATIONS

American Association for Cancer Research
American Association of Immunologists
American Society for Microbiology
American Association for the Advancement of Science

AD HOC EDITORIAL ACTIVITY

Journal of Immunology
JI: Cutting Edge
Journal of Clinical Investigation
Journal of Biological Chemistry
Proc. Natl. Acad. Sci. USA
Molecular and Cellular Biology
Oncogene
Journal of Cellular Physiology
Antiviral Chemistry & Chemotherapy
Blood

SELECTED INVITED PRESENTATIONS

Regulated association between the SH3 domain of the Emt/Itk tyrosine kinase and multiple intracellular ligands. Lymphocyte Signal Transduction Workshop, Santorini, Greece (October, 2000)

Signal transduction through the T-lymphocyte receptors CD2 and LFA-1. Sugen, South San Francisco, California (June, 1996)

Lymphocyte antigen receptor activation of a novel FAK-related tyrosine kinase substrate. Lymphocyte Activation Meeting, Keystone Symposia on Molecular and Cellular Biology, Keystone, Colorado (April, 1994)

T-cell signaling via integrin receptors and immunoglobulin-superfamily molecules. University of Chicago, Committee on Immunology Seminar Series, Chicago, Illinois (March, 1994)

T-cell signaling through integrins and Ig superfamily receptors. Seattle Biomedical Research Institute, Seminar Series, Seattle, Washington (March, 1993)

β_2-integrin signaling in T-cells through PLCγ1 is TCR-dependent. Keystone Symposium on Phosphorylation/Dephosphorylation in Signal Transduction, Keystone, Colorado (January, 1993)

Regulation of TCR-induced PLCγ1 tyrosine phosphorylation by CD45. Plenary seminar at Biochemical Immunology Group Colloquium on the Structure and Function of the Leukocyte Common Antigen CD45, Edinburgh, Scotland (September, 1991)

PATENTS AND INVENTIONS

Raitano, A., S. B. Kanner, P. Challita, J. J. Perez-Villar, W. Ge, and A. Jakobovits. Nucleic acids and corresponding proteins entitled 158P3D2 useful in treatment and detection of cancer. November, 2004

Kanner, S. B., A. Raitano, P. Challita, J. J. Perez-Villar, W. Ge, and A. Jakobovits. Nucleic acids and corresponding proteins entitled 58P1D12 useful in treatment and detection of cancer. August, 2004

Raitano, A., P. Challita, J. J. Perez-Villar, W. Ge, S. B. Kanner and A. Jakobovits. Nucleic acids and corresponding proteins entitled 109P1D4 useful in treatment and detection of cancer. April, 2004

Barrish, J. C., J. Das, S. B. Kanner, C. Liu, S. H. Spergel, J. Wityak, A. M. P. Doweyko, and J. A. Furch. Thiazolyl inhibitors of Tec family tyrosine kinases. US6706717; March, 2004

Jakobovits, A., R. K. Morrison, A. B. Raitano, P. M. Challita-Eid, J. J. Perez-Villar, K. J. M. Morrison, M. Faris, W. Ge, , J. Gudas and S. B. Kanner. Nucleic acid and corresponding protein named 158P1D7 useful in the treatment and detection of bladder and other cancers. WO-04072263-A2; February, 2004

Kanner, S. B., A. Raitano, A. Jakobovits, P. Challita-Eid, W. Ge, J. J. Perez-Villar and M. Faris. Nucleic acids and corresponding proteins entitled 254P1D6B useful in treatment and detection of cancer. US-20040214212-A1; January, 2004

Perez-Villar, J. J., H. Chang, W-P. Yang, Y. Wu, G. S. Whitney and S. B. Kanner. Identification and cloning of a full-length human Clnk-related gene, MIST (Mast Cell Immunoreceptor Signal Transducer). US-020155563-A1; October, 2002

Chang, H., W-P. Yang, Y. Wu, G. S. Whitney, J. J. Perez-Villar and S. B. Kanner. Cloning and expression of human SLAP-2: a novel SH2/SH3 domain-containing human SLAP homologue having immune cell-specific expression. WO-0242457-A1; May, 2002

Kanner, S. B., A. B. Reynolds, S. J. Parsons and J. T. Parsons. Monoclonal antibodies to $p125^{FAK}$, $p120^{ctn}$, cortactin, $pp60^{src}$ and tensin. Licensed and commercialized from the University of Virginia to Upstate/Cell Signaling Solutions; 1991

Kanner, S. B., A. B. Reynolds and J. T. Parsons. Monoclonal antibody 6G9 to phosphotyrosine. Licensed and commercialized from the University of Virginia to Covance, Inc./Berkeley Antibody Company; 1991

PUBLICATIONS

1. Parks, W. P., G. B. Scott, **S. B. Kanner**, E. S. Hubbell, M. A. Fischl, G. M. Dickinson and E. R. Schiff. (1984) Acquired immunodeficiency syndrome and human T-cell leukemia virus in Miami: a household approach. *In* Human T-cell Leukemia Viruses (R. C. Gallo, M. Essex, and L. Gross, eds.), Cold Spring Harbor Press, New York. *pp.* 381-391

2. **Kanner, S. B.**, C. Cheng-Mayer, R. B. Geffin, W. P. Parks, G. A. Beltz, L. O. Arthur, K. P. Samuel and T. S. Papas. (1986) Human retroviral *env* and *gag* polypeptides: serologic assays to measure infection. *J. Immunol.* **137**:674-678

3. **Kanner, S. B.**, E. S. Parks, G. B. Scott and W. P. Parks. (1987) Simultaneous infections with human T cell leukemia virus type I and the human immunodeficiency virus. *J. Inf. Dis.* **155**:617-625

4. **Kanner, S. B.**, S. J. Parsons, J. T. Parsons and T. M. Gilmer. (1988) Activation of pp60$^{c\text{-}src}$ tyrosine kinase specific activity in tumor-derived Syrian hamster embryo cells. *Oncogene* **2**:327-335

5. Reynolds, A. B., D. J. Roesel, **S. B. Kanner** and J. T. Parsons. (1989) Transformation-specific tyrosine phosphorylation of a novel cellular protein in chicken cells expressing oncogenic variants of the avian cellular *src* gene. *Mol. Cell. Biol.* **9**:629-638

6. **Kanner, S. B.**, T. M. Gilmer, A. B. Reynolds and J. T. Parsons. (1989) Novel tyrosine phosphorylations accompany the activation of pp60$^{c\text{-}src}$ during chemical carcinogenesis. *Oncogene* **4**:295-300

7. **Kanner, S. B.**, A. B. Reynolds and J. T. Parsons. (1989) Immunoaffinity purification of tyrosine-phosphorylated cellular proteins. *J. Immunol. Methods* **120**:115-124

8. Reynolds, A. B., **S. B. Kanner**, H-C. R. Wang and J. T. Parsons. (1989) Stable association of activated pp60^{src} with two tyrosine-phosphorylated cellular proteins. *Mol. Cell. Biol.* **9**:3951-3958

9. Ely, C. M., K. M. Oddie, J. S. Litz, A. J. Rossomando, **S. B. Kanner**, T. W. Sturgill, and S. J. Parsons. (1990) A 42 kD tyrosine kinase substrate linked to chromaffin cell secretion exhibits an associated MAP kinase activity and is highly related to a 42 kD mitogen-stimulated protein in fibroblasts. *J. Cell Biol.* **110**:731-742

10. **Kanner, S. B.**, A. B. Reynolds, R. R. Vines and J. T. Parsons. (1990) Monoclonal antibodies to individual tyrosine-phosphorylated protein substrates of oncogene-encoded tyrosine kinases. *Proc. Natl. Acad. Sci. USA* **87**:3328-3332

11. **Kanner, S. B.**, A. B. Reynolds and J. T. Parsons. (1991) Tyrosine phosphorylation of a 120-kDa pp60^{src} substrate upon epidermal growth factor and platelet-derived growth factor receptor stimulation and in polyomavirus middle-T-antigen-transformed cells. *Mol. Cell. Biol.* **11**:713-720

12. Bouton, A. H., **S. B. Kanner**, R. R. Vines, H-C. R. Wang, J. B. Gibbs and J. T. Parsons. (1991) Transformation by pp60^{src} or stimulation of cells with epidermal growth factor induces the stable association of tyrosine phosphorylated cellular proteins with GTPase activating protein. *Mol. Cell. Biol.* **11**:945-953

13. Bouton, A. H., **S. B. Kanner**, R. R. Vines and J. T. Parsons. (1991) Tyrosine phosphorylation of three cellular proteins correlates with transformation of rat 1 cells by pp60^{src}. *Mol. Carcinogenesis* **4**:145-152

14. **Kanner, S. B.**, A. B. Reynolds, H-C. R. Wang, R. R. Vines and J. T. Parsons. (1991) The SH2 and SH3 domains of pp60^{src} direct stable association with tyrosine-phosphorylated proteins p130 and p110. *EMBO J.* **10**:1689-1698

15. Wu, H., A. B. Reynolds, **S. B. Kanner**, R. R. Vines and J. T. Parsons. (1991) Identification and characterization of a novel cytoskeleton-associated pp60^{src} substrate. *Mol. Cell. Biol.* **11**:5113-5124

16. Ledbetter, J. A., **S. B. Kanner**, G. L. Schieven and J. Deans. (1991) Transmembrane signals in T cells: tyrosine phosphorylation regulates phospholipase C activation. *In* Signaling Mechanisms in Secretory and Immune Cells (J. R. Martinez, B. S. Edwards and J. C. Seagrave, eds.), San Francisco Press, California. *pp*. 51-56

17. **Kanner, S. B.**, T. J. Kavanagh, A. Grossmann, S-L. Hu, J. B. Bolen, P. S. Rabinovitch and J. A. Ledbetter. (1992) Sulfhydryl oxidation down-regulates T-cell signaling and inhibits tyrosine phosphorylation of phospholipase Cγ1. *Proc. Natl. Acad. Sci. USA* **89**:300-304

18. **Kanner, S. B.** and J. A. Ledbetter. (1992) CD45 regulates TCR-induced signalling through tyrosine phosphorylation of phospholipase Cγ1. *Biochem. Soc. Trans.* **20**:178-184

19. Turka, L. A., **S. B. Kanner**, G. L. Schieven, C. B. Thompson and J. A. Ledbetter. (1992) CD45 modulates T cell receptor/CD3-induced activation of human thymocytes via regulation of tyrosine phosphorylation. *Eur. J. Immunol.* **22**:551-557

20. **Kanner, S. B.**, J. P. Deans and J. A. Ledbetter. (1992) Regulation of CD3-induced phospholipase C-gamma1 (PLCγ1) tyrosine phosphorylation by CD4 and CD45 receptors. *Immunology* **75**:441-447

21. Deans, J. P., **S. B. Kanner**, R. M. Torres and J. A. Ledbetter. (1992) Interaction of CD4:lck with the T cell receptor/CD3 complex induces early signaling events in the absence of CD45 tyrosine phosphatase. *Eur. J. Immunol.* **22**:661-668

22. **Kanner, S. B.**, N. K. Damle, J. Blake, A. Aruffo and J. A. Ledbetter. (1992) CD2/LFA-3 ligation induces phospholipase-Cγ1 tyrosine phosphorylation and regulates CD3 signaling. *J. Immunol.* **148**:2023-2029

23. Sancho, J., J. A. Ledbetter, M-S. Choi, **S. B. Kanner**, J. P. Deans and C. Terhorst. (1992) CD3-ζ surface expression is required for CD4-p56^{lck}-mediated up-regulation of T cell antigen receptor-CD3 signaling in T cells. *J. Biol. Chem.* **267**:7871-7879

24. Gilliland, L. K., G. L. Schieven, N. A. Norris, **S. B. Kanner**, A. Aruffo and J. A. Ledbetter. (1992) Lymphocyte lineage-restricted tyrosine-phosphorylated proteins that bind PLCγ1 SH2 domains. *J. Biol. Chem.* **267**:13610-13616

25. Aruffo, A., **S. B. Kanner**, D. Sgroi, J. A. Ledbetter and I. Stamenkovic. (1992) CD22-mediated stimulation of T cells regulates TCR/CD3-induced signaling. *Proc. Natl. Acad. Sci. USA* **89**:10242-10246

26. **Kanner, S. B.**, N. Ødum, L. Grosmaire, S. Masewicz, A. Svejgaard and J. A. Ledbetter. (1992) Superantigen and HLA-DR ligation induce phospholipase-Cγ1 activation in class II^+ T-cells. *J. Immunol.* **148**:3482-3488

27. Kavanagh, T. J., A. Grossmann, J. C. Jinneman, **S. B. Kanner**, C. C. White, D. L. Eaton, J. A. Ledbetter and P. S. Rabinovitch. (1993) The effect of 1-chloro-2, 4-dinitrobenzene exposure on antigen receptor (CD3)-stimulated transmembrane signal transduction in purified subsets of human peripheral blood lymphocytes. *Toxicol. Appl. Pharmacol.* **119**:91-99

28. Ledbetter, J. A., J. P. Deans, A. Aruffo, L. S. Grosmaire, **S. B. Kanner**, J. B. Bolen and G. L. Schieven. (1993) CD4, CD8 and the role of CD45 in T-cell activation. *Curr. Opin. Immunol.* **5**:334-340

29. Ødum, N., **S. B. Kanner**, J. A. Ledbetter and A. Svejgaard. (1993) MHC class II molecules deliver costimulatory signals in human T cells through a functional linkage with IL-2-receptors. *J. Immunol.* **150**:5289-5298

30. Chalupny, N. J., **S. B. Kanner**, G. L. Schieven, S. Wee, L. K. Gilliland, A. Aruffo and J. A. Ledbetter. (1993) Tyrosine phosphorylation of CD19 in pre-B and mature B cells. *EMBO J.* **12**:2691-2696

31. **Kanner, S. B.**, L. S. Grosmaire, J. A. Ledbetter and N. K. Damle. (1993) β_2-integrin LFA-1 signaling through phospholipase-Cγ1 activation. *Proc. Natl. Acad. Sci. USA* **90**:7099-7103

32. Whitney, G. S., P-Y. Chan, J. Blake, W. L. Cosand, M. G. Neubauer, A. Aruffo and **S. B. Kanner.** (1993) Human T and B lymphocytes express a structurally conserved focal adhesion kinase ($pp125^{FAK}$). *DNA Cell Biol.* **12**:823-830

33. Parsons, M., J. A. Ledbetter, G. L. Schieven, A. E. Nel and **S. B. Kanner.** (1994) Developmental regulation of pp44/46, tyrosine-phosphorylated proteins associated with tyrosine/serine kinase activity in *Trypanosoma brucei. Mol. Biochem. Parasitol.* **63**:69-78

34. Chan, P-Y., **S. B. Kanner**, G. S. Whitney and A. Aruffo. (1994) A transmembrane-anchored chimeric focal adhesion kinase is constitutively activated and phosphorylated at tyrosine residues identical to $pp125^{FAK}$. *J. Biol. Chem.* **269**:20567-20574

35. Schieven, G. L., R. S. Mittler, S. G. Nadler, J. M. Kirihara, J. B. Bolen, **S. B. Kanner** and J. A. Ledbetter. (1994) ZAP-70 tyrosine kinase, CD45, and T cell receptor involvement in UV- and H_2O_2-induced T cell signal transduction. *J. Biol. Chem.* **269**:20718-20726

36. Dietsch, M. T., P-Y. Chan, **S. B. Kanner**, L. K. Gilliland, J. A. Ledbetter, P. S. Linsley and A. Aruffo. (1994) Coengagement of CD2 with LFA-1 or VLA-4 by bispecific ligand fusion proteins primes T cells to respond more effectively to T cell receptor-dependent signals. *J. Leukoc. Biol.* **56**:444-452

37. **Kanner, S. B.**, A. Aruffo and P-Y. Chan. (1994) Lymphocyte antigen receptor activation of a focal adhesion kinase-related tyrosine kinase substrate. *Proc. Natl. Acad. Sci. USA* **91**:10484-10487

38. Wong, S. C.-T., **S. B. Kanner**, J. A. Ledbetter, S. Gupta, G. Kumar and A. E. Nel. (1995) Evidence for LFA-1/ICAM-1 dependent stimulation of protein tyrosine phosphorylation in human B lymphoid cell lines during homotypic adhesion. *J. Leukoc. Biol.* **57**:343-351

39. **Kanner, S. B.** and O. K. Haffar. (1995) HIV-1 down-regulates CD4 costimulation of TCR/CD3-directed tyrosine phosphorylation through CD4/p56^{lck} dissociation. *J. Immunol.* **154**:2996-3005

40. Ohnishi, H., J. A. Ledbetter, **S. B. Kanner**, P. S. Linsley, T. Tanaka, A. M. Geller and M. Kotb. (1995) CD28 cross-linking augments TCR-mediated signals and costimulates superantigen responses. *J. Immunol.* **154**:3180-3193

41. Grossmann, A., P. S. Rabinovitch, T. J. Kavanagh, J. C. Jinneman, L. K. Gilliland, J. A. Ledbetter and **S. B. Kanner**. (1995) Activation of murine T-cells via phospholipase-Cγ1-associated protein tyrosine phosphorylation is reduced with aging. *J. Gerontol.* **50A**:B205-B212

42. Tarakhovsky, A., **S. B. Kanner**, J. Hombach, J. A. Ledbetter, W. Müller, N. Killeen and K. Rajewsky. (1995) A role for CD5 in TCR-mediated signal transduction and thymocyte selection. *Science* **269**:535-537

43. Nel, A. E., S. Gupta, L. Lee, J. A. Ledbetter and **S. B. Kanner**. (1995) Ligation of the T-cell antigen receptor (TCR) induces association of hSos1, ZAP-70, phospholipase C-γ1, and other phosphoproteins with Grb2 and the ζ-chain of the TCR. *J. Biol. Chem.* **270**:18428-18436

44. **Kanner, S. B.**, L. S. Grosmaire, J. Blake, G. L. Schieven, S. Masewicz, N. Ødum and J. A. Ledbetter. (1995) ZAP-70 and p72^{syk} are signaling response elements through MHC class II molecules. *Tissue Antigens* **46**:145-154

45. Das, A., G. C. Peterson, **S. B. Kanner**, U. Frevert and M. Parsons. (1996) A major tyrosine-phosphorylated protein of *Trypanosoma brucei* is a nucleolar RNA-binding protein. *J. Biol. Chem.* **271**:15675-15681

46. **Kanner, S. B.** (1996) Focal adhesion kinase-related fakB is regulated by the integrin LFA-1 and interacts with the SH3 domain of phospholipase Cγ1. *Cell. Immunol.* **171**:164-169

47. Ochs, H. D., Q. Zhu, T. Liu, C. Watanabe, **S. B. Kanner**, D. Hollenbaugh and A. Aruffo. (1996) Wiskott-Aldrich syndrome: The WAS protein, phenotype and genotype. *In* Progress in Immunodeficiency VI (A. Fasth and J. Bjorkander, eds.), Elsevier Science B.V., Goteborg, Sweden. *pp.* 85-96

48. Kotb, M., **S. B. Kanner** and J. A. Ledbetter. (1997) Biochemical analysis of TCR mediated signaling. *In* The Human Antigen T-cell Receptor: Selected Protocols and Applications (J. R. Oksenberg, ed.), R.G. Landes Company and Chapman & Hall, Texas. *pp.* 489-545

49. Ng, T. T. C., **S. B. Kanner**, M. J. Humphries, R. G. Wickremasinghe, K. E. Nye, J. Anderson, S. H. Khoo and W. J. W. Morrow. (1997) The integrin-triggered rescue of T lymphocyte apoptosis is blocked in HIV-1-infected individuals. *J. Immunol.* **158**:2984-2999

50. Scholler, J. K. and **S. B. Kanner**. (1997) The human p167 gene encodes a unique structural protein that contains centrosomin A homology and associates with a multicomponent complex. *DNA Cell Biol.* **16**:515-531

51. Lansing, T. J., B. F. Turk, **S. B. Kanner** and T. M. Gilmer. (1997) Mutational activation of $pp60^{c\text{-}src}$ leads to a tumorigenic phenotype in a preneoplastic Syrian hamster embryo cell line. *Cancer Res.* 57:1962-1969

52. Zhu, Q., C. Watanabe, T. Liu, D. Hollenbaugh, R. M. Blaese, **S. B. Kanner**, A. Aruffo and H. D. Ochs. (1997) The Wiscott-Aldrich syndrome/X-linked thrombocytopenia: WASP gene mutations, protein expression, and phenotype. *Blood* **90**:2680-2689

53. Brockdorff, J., **S. B. Kanner**, M. Nielsen, N. Borregaard, C. Geisler, A. Svejgaard and N. Ødum. (1998) Interleukin-2 induces β2-integrin-dependent signal transduction involving the focal adhesion kinase-related protein B (fakB). *Proc. Natl. Acad. Sci. USA* **95**:6959-6964

54. Loo, D. T., **S. B. Kanner** and A. Aruffo. (1998) Filamin binds to the cytoplasmic domain of the β1-integrin: identification of amino acids responsible for this interaction. *J. Biol. Chem.* **273**:23304-23312

55. Connelly, R. J., M. S. Hayden, J. K. Scholler, T. T. Tsu, B. Dupont, J. A. Ledbetter and **S. B. Kanner**. (1998) Mitogenic properties of a bispecific single chain Fv-Ig fusion generated from CD2-specific mAb to distinct epitopes. *Int. Immunol.* **10**:1863-1872

56. Ng, T. T. C., I. E. Collins, **S. B. Kanner**, M. J. Humphries, N. Amft, R. G. Wickremasinghe, D. D'Cruz, K. E. Nye and W. J. W. Morrow. (1999) Integrin signalling defects in T-lymphocytes in systemic lupus erythematosus. *Lupus* **8**:39-51

57. Perez-Villar, J. J., G. S. Whitney, M. A. Bowen, D. H. Hewgill, A. A. Aruffo and **S. B. Kanner**. (1999) CD5 negatively regulates the T-cell antigen receptor signal transduction pathway: involvement of SH2-containing phosphotyrosine phosphatase SHP-1. *Mol. Cell. Biol.* **19**:2903-2912

58. Perez-Villar, J. J. and **S. B. Kanner**. (1999) Regulated association between the tyrosine kinase Emt/Itk/Tsk and phospholipase-Cγ1 in human T lymphocytes. *J. Immunol.* **163**:6435-6441

59. Scholler, J. K., J. J. Perez-Villar, K. O'Day and **S. B. Kanner**. (2000) Engagement of the T-lymphocyte antigen receptor regulates association of son-of-sevenless homologues with the SH3 domain of phospholipase Cγ1. *Eur. J. Immunol.* **30**:2378-2387

60. van Seventer, G. A., H. J. Salmen, S. F. Law, G. M. O'Neill, M. M. Mullen, A. M. Franz, **S. B. Kanner**, E. A. Golemis and J. M. van Seventer. (2001) Focal adhesion kinase regulates β1 integrin-dependent T cell migration through an HEF1 effector pathway. *Eur. J. Immunol.* **31**:1417-1427

61. Perez-Villar, J. J., K. O'Day, D. H. Hewgill, S. G. Nadler and **S. B. Kanner**. (2001) Nuclear localization of the tyrosine kinase Itk and interaction of its SH3 domain with karyopherin α (Rch1α). *Int. Immunol.* **13**:1265-1274

62. Perez-Villar, J. J., G. S. Whitney, M. T. Sitnick, R. J. Dunn, S. Venkatesan, K. O'Day, G. L. Schieven, T. Lin and **S. B. Kanner**. (2002) Phosphorylation of the linker for activation of T-cells by Itk promotes recruitment of Vav. *Biochemistry* **41**:10732-10740

63. **Kanner, S. B.** and J. J. Perez-Villar. (2003) Altering T cell activation by targeting the multi-domain tyrosine kinase Itk. *Trends Immunol.* **24**:249-253

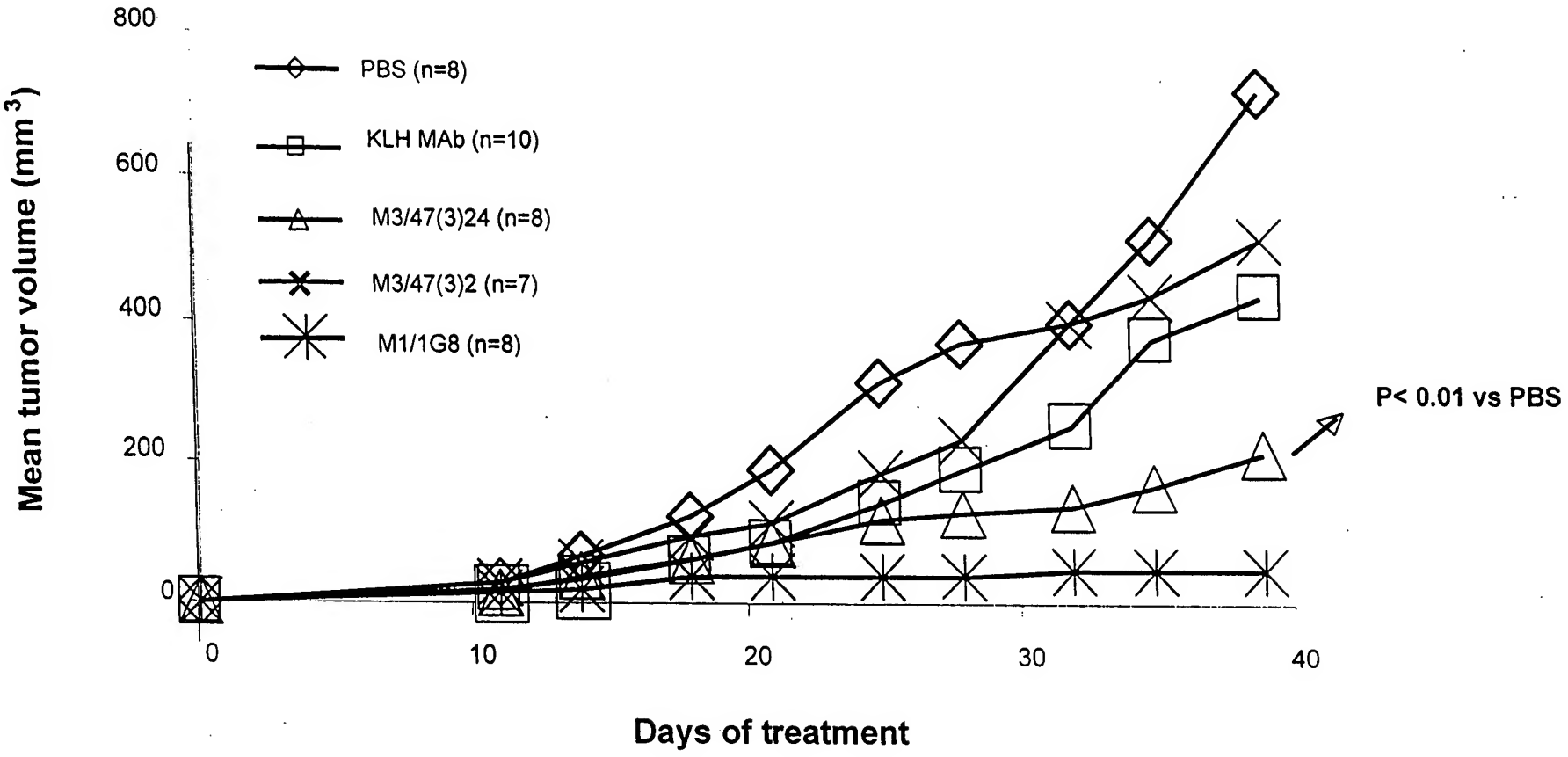
64. Wityak, J., J. Das, R. V. Moquin, Z. Shen, J. Lin, P. Chen, A. M. Doweyko, S. Pitt, S. Pang, D. R. Shen, Q. Fang, H. F. de Fex, G. L. Schieven, **S. B. Kanner** and J. C. Barrish. (2003) Discovery and initial SAR of 2-amino-5-carboxamidothiazoles as inhibitors of the Src-family kinase $p56^{Lck}$. *Bioorg. Med. Chem. Lett.* **13**:4007-4010

65. Chen, P., A. M. Doweyko, D. Norris, H. H. Gu, S. H. Spergel, J. Das, R. V. Moquin, J. Lin, J. Wityak, E. J. Iwanowicz, K. W. McIntyre, D. J. Shuster, K. Behnia, S. Chong, H. de Fex, S. Pang, S. Pitt, D. R. Shen, S. Thrall, P. Stanley, O. R. Kocy, M. R. Witmer, **S. B. Kanner**, G. L. Schieven and J. C. Barrish. (2004) Imidazoquinoxaline Src-family kinase p56Lck inhibitors: SAR, QSAR, and the discovery of (*S*)-*N*-(2-chloro-6-methylphenyl)-2-(3-methyl-1-piperazinyl)imidazo-[1,5-*a*]pyrido[3,2-*e*]pyrazin-6-amine (BMS-279700) as a potent and orally active inhibitor with excellent in vivo anti-inflammatory activity. *J. Med. Chem.* **47**:4517-4529

66. Lin, T., K. W. McIntyre, J. Das, C. Liu, K. D. O'Day, B. Penhallow, C-Y. Hung, D. J. Shuster, X. Yang, R. Townsend, J. Postelnek, S. H. Spergel, J. Lin, R. V. Moquin, J. A. Furch, A. V. Kamath, H. Zhang, P. H. Marathe, J. J. Perez-Villar, A. Doweyko, L. Killar, J. H. Dodd, J. C. Barrish, J. Wityak and **S. B. Kanner**. (2004) Selective Itk inhibitors block T-cell activation and murine lung inflammation. *Biochemistry* **43**:11056-11062

67. Leftheris, K., G. Ahmed, R. Chan, A. J. Dyckman, Z. Hussain, K. Ho, J. Hynes, Jr., J. Letourneau, W. Li, S. Lin, A. Metzger, K. J. Moriarty, C. Riviello, Y. Shimshock, J. Wen, J. Wityak, S. T. Wrobleski, H. Wu, J. Wu, M. Desai, K. M. Gillooly, T. H. Lin, D. Loo, K. W. McIntyre, S. Pitt, D. R. Shen, S. J. Shuster, R. Zhang, D. Diller, A. Doweyko, J. Sack, J. Baldwin, J. Barrish, J. Dodd, I. Henderson, **S. B. Kanner**, G. L. Schieven and M. Webb. (2004) The discovery of orally active triaminotriazine aniline amides as inhibitors of p38 MAP kinase. *J. Med. Chem.* **47**:6283-6291

Exhibit B: PHOR-1 MAb M3/47(3)24 Inhibits Growth of Human Prostate Cancer Xenograft in Mice



- Treatment started on the same day of tumor cell injection (2 million/mouse) MAbs were dosed i.p. at 250 µg twice a week for a total of 12 doses.